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SYNTHESIS, MOLECULAR DOCKING AND BIOLOGICAL EVALUATION OF DOPAMINE DERIVATIVES

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Abstract

Dopamine delivery to the central nervous system (CNS) undergoes the permeability limitations ofblood-brain barrier (BBB) which is a selective interface that excludes most water-soluble moleculesfrom entering the brain. Neutral amino acids permeate the BBB by specific transport systems. Condensationof dopamine with neutral amino acids could afford potential prodrugs able to interact with theBBB endogenous transporters and easily enter the brain. The synthesis and characterization of thedopamine derivative4-(2-Aminoethyl)benzene-1,2-diol Carbamodithiolatessynthesized from Dopamine and Carbon disulfide and further characterized. Docking studies showed that blocking the division of cancer cells and resulting in cell death. It is necessary to understand the binding properties in developing new potential Protein targeting against neurological disorders.

Key Words: Dopamine, Docking Studies, Carbamodithiolates, neurological disorders.

Introduction:

Insights gained from decades of research have begun to unlock the pathophysiology of these complex diseases and have provided targets for disease-modifying therapies. In the last decade, few therapeutic agents designed to modify the underlying disease process have progressed to clinical trials and none have been brought to market. With the focus on disease modification, biomarkers promise to play an increasingly important role in clinical trials. Among the histamine receptor subtypes, H3 receptors play an important regulatory role in the CNS. Activation of H3 auto receptors can inhibit histamine synthesis and release from histaminergic neurons[1,2], while activation of H3 hetero receptors can inhibit release of other neurotransmitters such acetylcholine, noradrenaline, dopamine and 5-HT from non-histaminergic neurons [3].

Conversely, blockade of H3 receptors with selective antagonists can increase the release of neurotransmitters involved in cognitive processes [4,5]. Selective H3 receptor antagonists have been shown to improve performance in a diverse range of rodent cognition paradigms [6], and can also increase wakefulness [7]. This has led to the development of H3receptor antagonists for the potential treatment of several CNS disorders including cognitive dysfunction in Alzheimer's disease (AD) [8].

Dopamine (3-hydroxytyramine hydrochloride) is a biogenic monoamine whichbelongs to a family of neurotransmitters called "catecholamines". These catecholaminesinclude several related neurotransmitters which are dopamine, norepinephrinealso known as noradrenalin, and epinephrine also known as adrenalin[1]. These neurotransmitters are considered to be unquestionably the most relevant to both normal and abnormal behaviour [1]. Dopamine is a neurotransmitterthat can produce a myriad of actions on neurons either directly or throughG-protein-coupled receptors and is inactivated primarily through its reuptake bythe dopamine transporter back into presynaptic terminals of neurons shortly afterits release [1] [2]. Thus, it is not a fast-acting neurotransmitter. Dopamine isfound in the kidney peripherally and has many functions or applications dependingon the receptor involved. These include; voluntary movements, regulategrowth and development, regulations of feeding, sleep, impulse control, reproductivebehaviours, working memory, learning, control of rennin in kidney (D1),renal functions, gastrointestinal motility, regulate locomotion-presynaptic receptorsinhibit locomotion and post synaptic receptors activate locomotion (D2),involved in endocrine function cognitions, emotions, regulations of locomotorfunctions and modulates endocrine functions (D3). Therapeutically, dopamineis indicated for the correction of hemodynamic imbalances present in the shocksyndrome due to myocardial infarctions, trauma, endotoxic septicaemia and open-heart surgery [3].

Protein-ligand binding Studies involved in neurological disorders of the Dopamine derivative, of new Carbamodithiolates is very scarce. Hence the present studies carried out a research program and analyzed the importance of Protein binding studies of the new Dopamine derivatives (Carbamodithiolates).

Parkinson's disease (PD) is one of the most common diseases of the central nervous system (CNS). It is frequently heralded by speech disturbances, which are one of its first symptoms. Parkinson's disease (PD) is a progressive extra pyramidal motor disorder. Pathologically, this disease is characterized by the selective dopaminergic (DAergic) neuronal degeneration in the substantia nigra. Correcting the DA deficiency in PD with levodopa (Ldopa) significantly attenuates the motor symptoms; however, its effectiveness often declines, and L-dopa-related adverse effects emerge after long-term treatment. Nowadays, DA receptor agonists are useful medication even regarded as first choice to delay the starting of L-dopa therapy. In advanced stage of PD, they are also used as adjunct therapy together with L-dopa. DA receptor agonists act by stimulation of presynaptic and postsynaptic DA receptors. Despite the usefulness, they could be causative drugs for valvopathy and nonmotor complication such as DA dysregulation syndrome (DDS).

Over the past decade, the Protein-ligand binding metal complexes have been extensively studied as DNA structural probes, DNA-dependent electron transfer probes, DNA foot printing and sequence-specific cleaving agents and potential anticancer drugs. The numerous biological experiments performed so far suggest that DNA is the primary intracellular target of anticancer drugs because the interaction between small molecules and DNA can cause DNA damage in cancer cells, blocking the division of cancer cells and resulting in cell death. It is necessary to understand the binding properties in developing new potential Protein targeting against neurological disorders.

MATERIALS AND METHODS

Experimental Section

Dopamine and carbon di sulfide were purchased from Aldrich. Other chemicals used were of analytical reagent or higher purity grade. Solvents used were of reagent grade and purified before use by the standard methods. Conductivity measurement was carried out by a Systronics conductivity bridge 305, using a conductivity cell of cell constant 1.0 double distilled water was used as solvent. Electronic absorption spectra on JAS.CO UV/VIS-7850 recording spectrophotometer. Infrared spectra was recorded on a JAS.Co-460 plus FT-IR spectrophotometer in the range of 4000-400 cm^{-1} in KBr pellets. Micro chemical analysis of carbon, hydrogen and nitrogen for the complexes were carried out on a Herause CHNO-Rapid elemental analyzer.^{1}H NMR spectra were recorded on a Brucker DRX-500 Advance spectrometer at 500MHz in DMSO-discussing tetra methyl silane as internal reference standard. Melting points were measured on a unimelt capillary melting Point apparatus and reported uncorrected.

Preparation of Sodium salt of Dopamine Derivative Carbamodithiolate

0.05 mol of amine was dissolved in 30 ml of absolute alcohol in a clean beaker which was placed in ice bath. To this cold solution add 5 ml of Sodium hydroxide (10N) solution, and then add Pure carbon disulphide (0.05ml) in drop wise with constant stirring. The contents were stirred mechanically for about 30 min, sodium salt of Carbamodithiolate precipitated out. It was dried over and recrystallized from ethanol.

RESULTS AND DISCUSSION

Infrared Spectrum

The characteristic band at 1440.06$cm^{-1}$was assignable to υ (N-CSS); this band defines a carbon Nitrogen bond order between a single bond (υ =1250-1350cm^{-1}) and a double bond (υ = 1640–1690cm^{-1}). The appearance of a band in that region 1641 cm^{-1} indicates that, of the three possible resonance structures reported by Chart *et al*., characterized by a strong delocalization of electrons in the carbamodithiolate moiety.A single sharp band at 900.81 cm^{-1} was assigned to the stretching vibrations of the C-S bond. The band at 3596.2 $cm^{-1}$and 3832.9 cm^{-1} associated with the υ(OH) υ (N-H) stretching vibrations. The characteristic absorption band at 1634.7cm^{-1} indicates aromatic stretching vibration. The absorption band appeared in between the region of 1265–634.2 cm^{-1} (C–C, C–O, C–N).

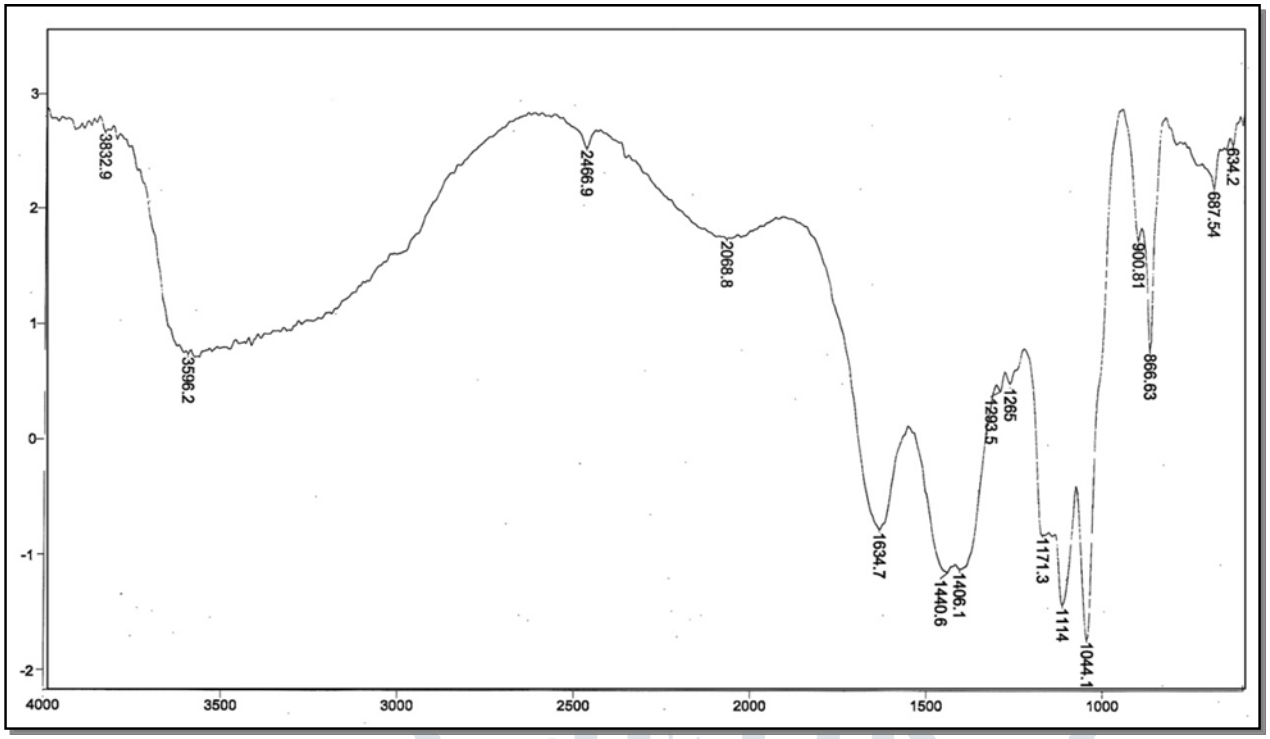

Fig.1.IR spectrum of Dopamine Carbamodithiolate compound

[1]HNMR spectrum

[1]HNMR spectra of ligand and metal complexes were recorded on av–400 MHz [1]HNMR Spectrometer in HCU in Hyderabad HI in $CDCl_3$solvent.[1]HNMRspectra of the Dopamine Carbamodithiolates gives the characteristic[1]HNMR spectrum. Two O-H protons on the benzene ring of Carbamodithiolate forms two singletsappear at 4.9-5.1 ppm. The predominantsinglet appeared in the region of 7.6 ppm due to NH proton in Dopamine Carbamodithiolate.

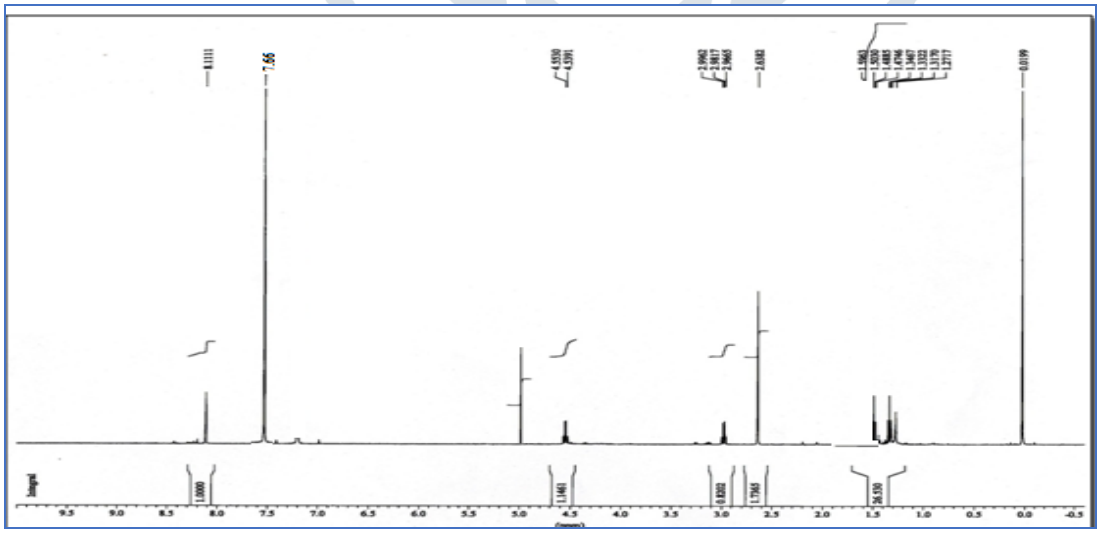

Fig.2.[1]HNMR spectrum of Dopamine Carbamodithiolate compound

Docking Studies:

Docking techniques, designed to find the correct conformation of a ligand and its receptor, have now been used for decades. The process of binding a small molecule to its protein target is not simple; several

entropic and enthalpic factors influence the interactions between them. The mobility of both ligand and receptor, the effect of the protein environment on the charge distribution over the ligand and their interactions with the surrounding water molecules, further complicate the quantitative description of the process. The idea behind this technique is to generate a comprehensive set of conformations of the receptor complex, and then to rank them according to their stability. The most popular docking programs include DOCK, AutoDock, FlexX, GOLD, and GLIDE among others.

In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex Lengauer T, Rarey M . Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using, for example, scoring functions. Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site. Characterization of the binding behavior plays an important role in rational design of drugs as well as to elucidate fundamental biochemical processes (Kitchen DB et al., 2004). During the course of the docking process, the ligand and the protein adjust their conformation to achieve an overall "best-fit" and this kind of conformational adjustment resulting in the overall binding is referred to as "induced-fit". Molecular docking research focusses on computationally simulating the molecular recognition process. It aims to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized.

A binding interaction between a small molecule ligand and an enzyme protein may result in activation or inhibition of the enzyme. If the protein is a receptor, ligand binding may result in agonism or antagonism. Docking is most commonly used in the field of drug design - most drugs are small organic molecules, and docking may be applied to: hit identification – docking combined with a scoring function can be used to quickly screen large databases of potential drugs in silico to identify molecules that are likely to bind to protein target of interest (see virtual screening). Lead optimization – docking can be used to predict in where and in which relative orientation a ligand binds to a protein (also referred to as the binding mode or pose). This information may in turn be used to design more potent and selective analogs. Bioremediation – Protein ligand docking can also be used to predict pollutants that can be degraded by enzymes.

The present work all the calculations were performed on a workplace by AMD 64 bits dual processing hi end server machines. Molecular docking calculations were performed with AutoDock 4.0. If not otherwise stated, default settings were used during all calculations. Dopamine carbamodithiolate (DCDT).

Materials and Methods:

Keeping the aim of constructing novel ligand complexes for H3, a library of 10 molecules was synthesized. The Auto Dock 4.0/ADT (Laskowski RA et al., 2005) program was used to investigate ligand binding to structurally refined H3 model using a grid spacing of 0.375 Å and the grid points in X, Y and Z axis were set to 60×60×60. The search was based on the Lamarckian genetic algorithm (Oprea TI et al., 2001) and the results were analyzed using binding energy. For each ligand, a docking experiment consisting of 100 stimulations was performed and the analysis was based on binding free energies and root mean square deviation (RMSD) values. Substrate docking with synthesized substrates was also performed on to H3 model with same parameters and PMV 1.4.5 viewer was then used to observe the interactions of the docked compounds to the H3 model.

Results and Discussion:

Binding energy for each docking was calculated using a semi-empirical free energy force field. Out of these 5 docked ligands and its Complexes molecules with receptor, top two molecules were filtered out on the

basis of binding energy. The binding modes and geometrical orientation of all compounds were almost identical, suggesting that all the inhibitors occupied a common cavity in the receptor. The binding energy of top three inhibitor molecules with an active site of receptor protein is given in Table 1.

Table-I Summary of docking results high ranked ligands and complex molecules with H3 receptor.

S. No	Compound Name	Receptor Name	Cluster Rank	RMSD	Lowest binding Energy (Kcal/mole)
1	Dopamine (DCDT) Ligand	H3 Receptor	1	0.00	-4.41

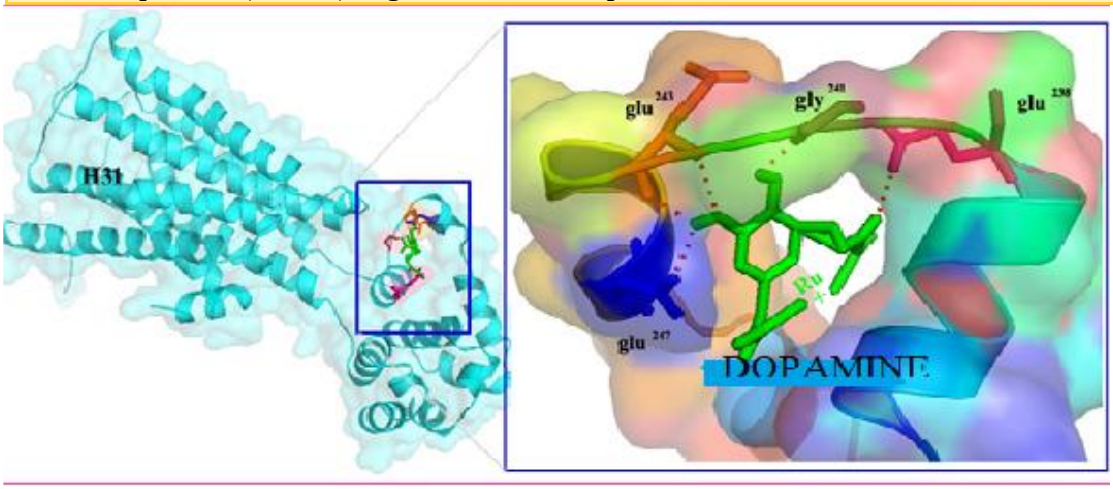

fig. -I The cortoon and electrostatic surface representation of the binding site of (e1,e2) H3 receptor model in sky blue, Dopamine derivative with sticks in green and amino acids same in e1and e2 that are represented Glu 238 in pink, Glu 241in limon, Glu 243 in orange and Glu 247 in blue colour.

Most docked inhibitors interacted by the same mode of the inhibitors, histamine H3 receptor binding site. The different surface pocket for residue seems to be an important factor in determining the binding mode of Dopamine derivativeof Glu 241 and Leu 231 amino acid residues (Figure 1a), Sythesised ligand metal complexes are showing same interaction and binding pose with high energy values.

Conclusion:

Dopamine Carbamodithiolates with have been synthesized and characterized. In this Study, we have docking studies of H3 receptor model with carbamodithiolateshaving more favorable rank score, docking score and hydrogen bonding energy and the binding pocket of the H3 receptor. Activation of H3 hetero receptors can inhibit release of other neurotransmitters such acetylcholine, noradrenaline, dopamine, conversely blockade of H3 receptors with our synthesized selective antagonists can increase the release of neurotransmitters involved in cognitive processes. Docking studies of carbamodithiolateswith H3 receptor and detailed analyses of inhibitors, H3 receptor interactions were done and the residues in binding responsible for binding to the inhibitors ofsubstrates with high binding affinity were identified. Hence, we conclude that these carbamodithiolatescould be a potential anti-Neurological disorderslead molecules for modulating the expression of H3 receptor in Parkinson's disease (PD) and Alzheimer's disease (AD) supports for experimental testing.

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